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Title

Admission Blood Pressure and Outcome of Endovascular Therapy: Secondary Analysis of ASTER trial

Brief Title: *Anadani M et al.; Admission Blood Pressure and Outcome*

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*A list of ASTER Trial Investigators is given in the Appendix.

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Abstract

Background-Elevated blood pressure (BP) is common among patients presenting with acute ischemic stroke due to large vessel occlusions. The literature is inconsistent regarding the association between admission BP and outcome of mechanical thrombectomy (MT). Moreover, it is unclear whether the first line thrombectomy strategy (stent retriever versus contact aspiration) modifies the relationship between BP and outcome.

Methods-This is a post hoc analysis of the ASTER (Contact Aspiration Versus Stent Retriever for Successful Revascularization) randomized trial. BP was measured prior to randomization in all included patients. Co-primary outcomes included 90-day functional independence (modified Rankin Scale [mRS] 0-2) and successful revascularization (modified Treatment in Cerebral Ischemia [mTICI] 2b-3). Secondary outcomes included symptomatic intracerebral hemorrhage (sICH) and parenchymal hemorrhage (PH) within 24 hours.

Results-A total of 381 patients were included in the present study. Mean (SD) systolic BP (SBP) and diastolic BP (DBP) were 148 (26) mm Hg and 81 (16) mm Hg, respectively. There was no association between SBP or DBP and successful revascularization or 90-day functional independence. Similarly, there was no association between admission SBP or DBP with sICH or PH. Subgroup analysis based on the first-line thrombectomy strategy revealed similar results with no heterogeneity across groups.

Conclusion-Admission BP was not associated with functional, angiographic or safety outcomes. Results were similar in both contact aspiration and stent-retriever groups.

Introduction

Blood pressure (BP) is commonly elevated in patients presenting with acute ischemic stroke.^{1,2} BP elevation can be secondary to physiological or psychological stressors related to ischemia, autonomic dysfunction, and elevated intracranial pressure.¹ There is a considerable evidence supporting the association between both high and low BP and poor functional outcome after acute ischemic stroke suggesting a U-shaped relationship.³⁻⁵ The optimal systolic blood pressure (SBP) level differed between studies and ranged from 120 mm Hg to 180mm Hg.^{4,5,6} However, most of the current evidence is derived from studies that included patients not treated with mechanical thrombectomy (MT). Studies including patients treated with MT have reported conflicting results, while two studies demonstrated an association between BP and functional outcome.^{6,7} A more recent large multicenter study failed to demonstrate a significant association between admission SBP and functional outcome after successful revascularization.⁸

Interestingly, previous studies suggested an association between higher BP and lower odds of successful revascularization after intra-arterial or intravenous reperfusion therapies.^{7 9 10} However, previous studies were limited by retrospective design or using older generation devices. Moreover, none of the previous studies assessed the effect of the first line strategy (contact aspiration vs. stent-retriever) on the relationship between BP and clinical or angiographic outcomes of MT. In addition, none of the previous studies assessed the association between clot burden score and BP on admission. Theoretically, the association between higher BP and lower revascularization can be merely an effect of higher clot burden.

In view of the inconsistency of the available literature and the lack of data regarding the effect of the first-line strategy on the relationship between BP and outcome, we performed a post hoc analysis of the ASTER (Contact Aspiration Versus Stent Retriever for Successful

Revascularization) randomized trial to investigate: 1) the association between baseline BP and angiographic and clinical outcomes; 2) the correlation between baseline BP and clot burden score; 3) the correlation between baseline BP and initial infarct volume and infarct extension; and 4) the effect of the first-line strategy on the association between BP and angiographic and clinical outcomes.

Methods

The authors declare that all supporting data are available within the article.

Patient Population

The ASTER trial protocol was previously reported.¹¹ In brief, ASTER was a randomized, multicenter, open-label, blinded end point clinical trial of first-line stent retriever (SR) versus first-line contact aspiration (CA). ASTER trial enrolled adult patients presenting with acute ischemic stroke due to anterior circulation proximal large vessel occlusions (carotid terminus, M1 or M2 segments of the middle cerebral artery) within 6 hours of symptoms onset. After baseline brain imaging, patients were randomized in 1:1 fashion to undergo either CA or SR thrombectomy.

BP was recorded on admission using a blood pressure cuff. The trial protocol did not specify any BP goal prior to MT except in case of intravenous thrombolysis. The study protocol and the consent form were approved by the Comité de Protection des Personnes Ile de France VI (ID 2015- A00830-49). Oral informed consent was obtained from patients if they had adequate level of consciousness to make a medical decision or, if not, from a surrogate decision maker.

Data analysis

All patients underwent magnetic resonance imaging (MRI) or computed tomography (CT) on admission and at 24 hours. Baseline MRI DWI (diffusion weighted imaging) volume was available for 141 patients.

All patients underwent magnetic resonance angiography (MRA) or CT angiogram (CTA) on admission. Clot burden score was scored on MRA or CTA on a scale from 0 to 10 by an independent core laboratory operator as described before.¹²

Study Outcomes

Coprimary outcomes of this study were functional independence at 90 days and successful revascularization at the end of procedure. Functional independence was defined as modified Rankin Scale (mRS) score of 0-2 at 90-days. Successful revascularization was defined as a modified Treatment In Cerebral Ischemia (mTICI) 2b-3 at the end of the procedure. Secondary outcomes included symptomatic intracerebral hemorrhage (sICH) according to European Cooperative Acute Stroke Study (ECASS) III criteria¹³, and parenchymal hemorrhage (PH) according to ECASS radiologic criteria¹⁴. In addition, we sought to study the association between BP and diffusion-weighted imaging (DWI) infarct volume on admission, admission ASPECTS (Alberta Stroke Program Early Computed Tomography Score) and 24-hour DWI infarct extension. The 24-hour DWI infarct extension was calculated by subtracting 24-DWI from admission DWI volume.

Statistical Analysis

Quantitative variables are expressed as means (standard deviation, SD) in the case of normal distribution or medians (interquartile range) otherwise. Categorical variables are expressed as numbers (percentage). Normality of distributions was assessed using histograms and the Shapiro-Wilk test.

We assessed the association of systolic and diastolic blood pressure at admission with outcomes (successful reperfusion, favorable outcome, symptomatic hemorrhage and parenchymal hematoma) using mixed logistic regression models taking into account center as random effect and ASTER treatment arm (contact aspiration vs. stent retriever as first-line strategy). Blood pressures (systolic and diastolic) on admission were first analysed as 4-level categorical variables according to quartiles (to appreciate the shape of the associations) and as continuous variables. Odds ratios (ORs) of each outcome with their 95% confidence intervals (CIs) were calculated for the upper quartiles relative to the lowest, or for 10 mmHg increase. We used multivariable mixed logistic regression models to adjust the associations, in addition to center and first line strategy for the following pre-specified confounders: age, pre-treatment NIHSS and ASPECT scores, and intravenous thrombolysis.

We assessed heterogeneity in associations of blood pressure at admission with outcomes (successful reperfusion, favorable outcome, symptomatic hemorrhage and parenchymal hematoma) according to first line strategy, by including the corresponding multiplicative term into the multivariable mixed logistic regression models. Finally, we assessed the association of blood pressure values with admission DWI volume, admission ASPECTS and admission clot burden score by calculating the Pearson's correlation coefficients (with 95% confidence intervals) after applying a log transformation for DWI volume and clot burden score.

Statistical testing was performed at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

Results

A total of 381 patients (mean age was 70 years, 54% patients were male, 61.1% had hypertension, and 17.2% had diabetes) were included in this study. Baseline characteristics of study cohort are reported in **Table 1**. Mean SBP and DBP were 148 ± 26 mm Hg and 81 ± 16 mm Hg, respectively.

As a continuous variable, SBP was not associated with successful revascularization or functional independence. When divided into quartiles (<130 , 130-143, 145-160 and >160 mm Hg), there was trend toward higher odds of successful revascularization with higher SBP; however, this association did not reach significance (**Table 2**). DBP was not associated with successful revascularization or favorable outcome whether it was treated as continuous or categorical (**Table 3**).

There was no correlation between admission SBP and admission ASPECTS ($r=0.03$; 95%CI, -0.08 to 0.13). In the subgroup of patients who had DWI acquisition on admission, there was no correlation between admission SBP and DWI lesion volume ($r=-0.16$; 95% CI -0.31 to 0.008, $n=141$) (**Figure 1**). Similarly, there was no correlation between admission SBP and clot burden score ($r=-0.08$, 95% CI -0.20 to 0.04, $N=242$). Similar results were observed for DBP ($r=-0.02$, 95%CI -0.12 to 0.09 for ASPECT, $r=-0.04$; 95% CI -0.81 to 0.12, $n=141$ for DWI lesion and $r=0.02$; 95% CI -0.11 to 0.14, $n=242$ for clot burden score).

In contrast, there was a positive correlation between DWI infarct extension and SBP ($r=0.28$; $P=0.016$. $N=57$) (**Figure 2**) but not with DBP ($r=0.13$; $P=0.26$; $N=57$).

With respect to safety outcomes, neither SBP nor DBP were associated with PH or SICH (**Tables 2 and 3**). Subgroup-analysis based on first-line strategy demonstrated similar results with no evidence of heterogeneity across subgroups (**Figure 3**).

Discussion

In this post hoc analysis of the ASTER trial, we did not find an association between hospital admission SBP or DBP with functional, angiographic or safety outcomes. Moreover, the first line thrombectomy strategy did not affect the relationship between BP and clinical outcomes.

Blood Pressure and Clinical Outcome

Previous studies of patients treated with MT reported conflicting results. A retrospective study including 116 patients demonstrated an association between higher SBP on admission and lower odds of functional independence.⁷ Similarly a post hoc analysis of MR CLEAN (A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke) trial demonstrated a U-shaped association between SBP and functional outcome with nadir at 120 mm Hg.⁶ However, a subsequent study of 1,245 patients with successful revascularization did not find association between admission SBP and functional outcome at 90 days.^{8, 15} In accordance with the later study, we did not find an association between SBP or DBP with 90-day functional outcome. The results were similar whether BP was considered as a continuous or categorical variable. Furthermore, we did not find a correlation between SBP or DBP and admission ASPECTS or admission DWI volume lesion. Therefore, our results do not support the hypothesis that high BP on admission is an effect of larger infarct volume. Despite that there was a statistically

significant correlation between admission BP and 24- hour infarct extension, the correlation was weak ($r=0.28$).

Blood Pressure and Revascularization

Pooled analysis of the of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Trials demonstrated an association between SBP and revascularization (<150mmHg vs. ≥ 150 mmHg; OR 0.42; 95% CI, 0.26 to 0.70; $P=0.0007$)¹⁶, a finding that was supported by a more recent retrospective study and meta-analysis of patients treated with MT .⁷
¹⁰ Multiple hypotheses were proposed to explain the effect of BP on revascularization.^{17, 18} One hypothesis suggested that the effect of SBP on revascularization is related to trans-clot pressure gradient created by opposing hydromechanical forces (defined by anterograde flow proximal to the occlusion versus retrograde leptomeningeal collateral flow); another hypothesis suggested that SBP is an effect of higher clot burden which in turn is associated with lower rate of revascularization.^{16, 17} In this study, we did not find an association between SBP or DBP and successful revascularization. In addition, we did not find a correlation between SBP on admission and clot burden score refuting the hypothesis that the association between high SBP and poor revascularization is related to high clot burden score.

First Line Strategy and Blood Pressure

To our knowledge, this is the first study reporting the effect of the first-line thrombectomy strategy on the relationship between BP and outcome. SR was linked to more endothelial cellular damage than contact aspiration devices¹⁸; therefore, theoretically high BP can exert a more harmful effect after SR. Conversely, CA technique is dependent on aspiration forces applied by

aspiration catheters on the clot¹⁹; therefore, BP's effect on revascularization could be more prominent in the CA technique than SR. In this study, BP was not associated with functional, angiographic or safety outcomes in both CA and SR groups and we did not find any evidence of heterogeneity between both treatment groups.

Taken together, our study did not suggest an association between admission blood pressure and MT clinical or efficacy outcomes. However, whether altering BP prior to MT affects the outcome remains an unanswered question in the absence of randomized clinical trials. The latest American Heart Association/American Stroke Association (AHA/ASA) guidelines recommended maintaining BP $\leq 185/110$ ²⁰ prior to MT, a recommendation that was driven mainly from the fact that most clinical trials evaluating the benefit of MT excluded patients with BP $> 185/110$. This recommendation was questioned by Mulder et al. and his colleagues due to lack of sufficient evidence to support such recommendations and more importantly due to concern that lowering BP prior to thrombectomy could delay MT and could be potentially harmful in patients with already compromised blood flow to ischemic brain.²¹ Future studies are needed to determine the best BP target before, during and after MT.

Limitations

Our study has limitations that need to be taken into account while interpreting our results. Similar to previous studies our BP measurement is based on a single pre-treatment reading which could reflect inaccurate representation of pre-treatment BP course. Data regarding vasoactive treatment prior to MT was not available for this study. Notably, except in case of thrombolysis, lowering BP prior to MT was not a common practice in the ASTER participating centers.

Conclusion

Our study did not demonstrate an association between admission BP and clinical or angiographic outcomes in patients receiving mechanical thrombectomy for acute ischemic stroke. Moreover, the first-line strategy did not affect the relationship between blood pressure and mechanical thrombectomy outcome.

Appendix

ASTER Trial (Contact Aspiration Versus Stent Retriever for Successful Revascularization)

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Figure legends

Figure 1. Scatter plot between systolic blood pressure and DWI lesion at admission

Figure 2: Scatter plot between systolic blood pressure at baseline and 24 hours change in DWI lesions

Figure 3: Effect of blood pressure on outcomes according to first-line strategy (ASTER treatment arms). Model 1 adjusted for center; Model 2 adjusted for center, age, NIHSS, ASPECTS and IV-tPA. Odds ratio calculated per 10 mmHg increase. P-het indicates P-value of heterogeneity in the association between blood pressure and outcomes according to first-line thrombectomy strategy.

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Disclosures

Dr Lapergue received a significant (>\$10K or 5%) research grant for ASTER Trial (Contact Aspiration Versus Stent Retriever for Successful Revascularization) and had modest (<\$10K or <5%) speaking engagements. The other authors report no conflicts.

Authors contributions:

All authors have: provided a substantial contribution to the conception and design of the studies and/or the acquisition and/or the analysis of the data and/or the interpretation of the data. They have drafted the work or revised it for significant intellectual content and approved the final version of the manuscript. They agree to be accountable for all aspects of the work, including its accuracy and integrity.

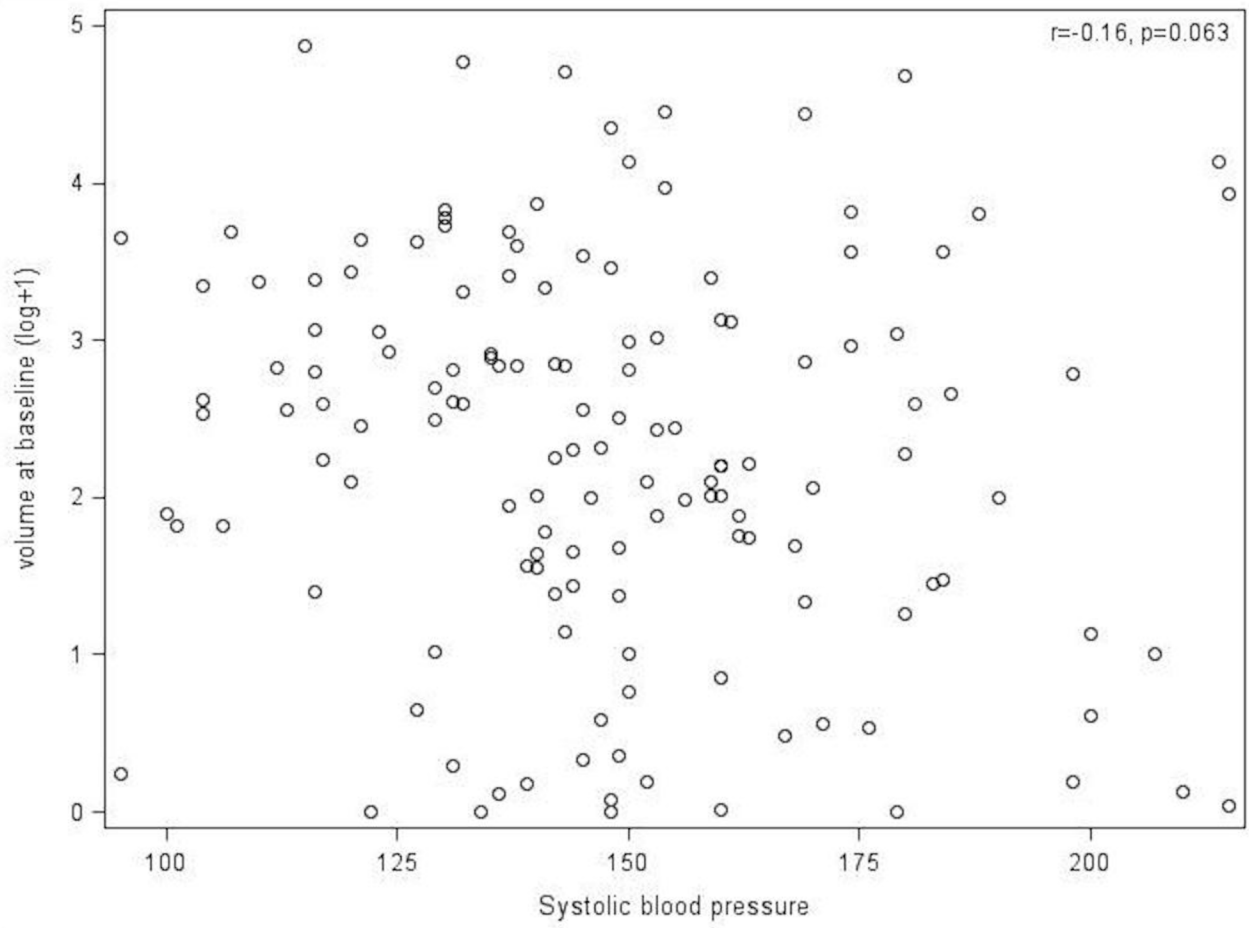
Data sharing statement: Additional data from this project can be acquired by contacting the corresponding author.

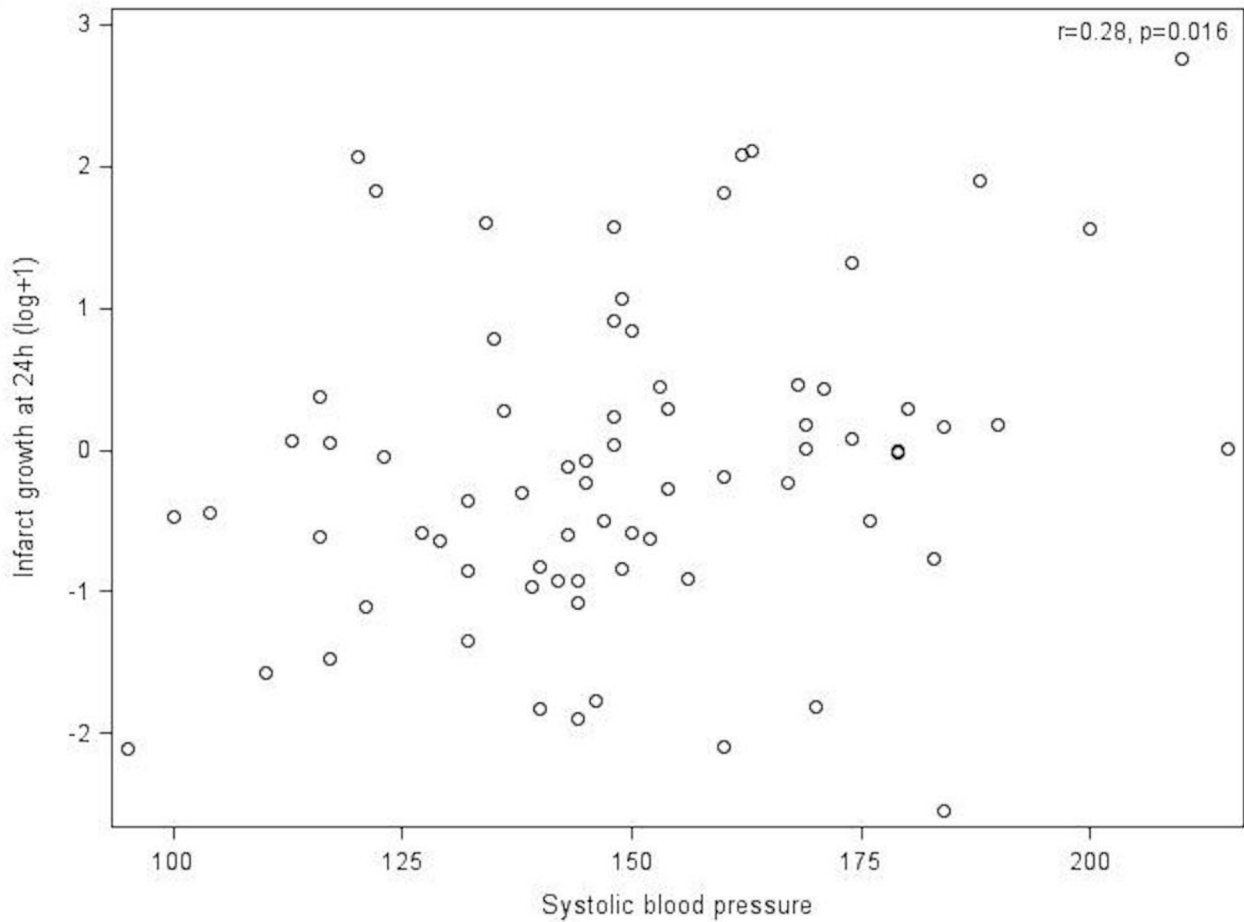
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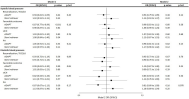


Table 1. Baseline characteristics in ASTER trial

Characteristics	
Age, y mean \pm SD	69.9 \pm 14.3
Men	207/381 (54.3)
Direct admission	138/381 (36.2)
Systolic blood pressure, mean \pm SD ^a	147.5 \pm 25.6
Diastolic blood pressure, mean \pm SD ^a	80.6 \pm 16.3
Medical history	
Hypertension	226/370 (61.1)
Diabetes	76/371 (20.5)
Hypercholesterolemia	131/367 (35.7)
Current smoking	62/244 (25.4)
Previous antithrombotic medications	
Antiplatelet use	118/367 (32.2)
Anticoagulations	71/367 (19.3)
Coronary artery disease	63/366 (17.2)
Previous stroke or TIA	65/372 (17.5)
Current stroke event	
NIHSS score, median (IQR) ^b	18.0 (12.0 to 20.0)
ASPECTS, median (IQR) ^c	7.0 (6.0 to 9.0)
Pre-stroke rankin \geq 1	62/379 (16.4)
Site of occlusion	
M1-MCA	204/381 (53.5)
M2-MCA	79/381 (20.7)
Intracranial ICA	55/381 (14.4)
Other ^c	43/381 (11.3)
Suspected stroke cause	

Large-artery atherosclerosis	30/381 (7.9)
Cardio-embolic	161/381 (42.3)
Others	190/381 (49.9)
DWI volume at admission, median (IQR) ^d	10.6 (3.3 to 26.6)
Clot burden score at admission ^e	
Endovascular treatment	
Onset to groin puncture, min, median (IQR) ^f	225.0 (180.0 to 280.0)
Onset to imaging	113.0 (83.0 to 150.0)
Imaging to groin puncture	106.0 (64.0 to 148.0)
General anesthesia	46/379 (12.1)
First-line CA strategy (ADAPT)	192/381 (50.4)

Values expressed as no/total no. (%) unless otherwise indicated.

^a 19 missing values, ^b 4 missing values, ^c 5 missing values, ^d 233 missing values, ^e 127 missing values, ^f 12 missing values.

Abbreviations: ASPECTS= Alberta stroke program early computed tomography score, CA=contact aspiration, ICA=intracranial carotid artery, IQR=interquartile range, IVT=intravenous thrombolysis, MCA=middle cerebral artery, MT=mechanical treatment, NIHSS=national institutes of health stroke scale, SD=standard deviation, TIA=transient ischemic attack.

Table 2. Effect of Systolic blood pressure on main outcomes

	SBP quartiles				p-value ^c	OR (95%CI) ^d	p-value ^e
	<130	130-145	145-160	>160			
Revascularization, TICI2b3							
N (%)	82/104 (78.8)	80/90 (88.9)	76/85 (89.4)	83/102 (81.4)			
OR (95%CI) ^a	1.00 (ref)	2.42 (1.05 to 5.60)	2.38 (1.00 to 5.67)	1.04 (0.51 to 2.13)	0.054	1.01 (0.89 to 1.13)	0.95
OR (95%CI) ^b	1.00 (ref)	2.42 (1.03 to 5.70)	2.37 (0.97 to 5.79)	1.13 (0.53 to 2.44)	0.082	1.01 (0.89 to 1.15)	0.85
Favorable outcome							
N (%)	46/86 (53.5)	39/83 (47.0)	35/77 (45.5)	40/94 (42.5)			
OR (95%CI) ^a	1.00 (ref)	0.70 (0.38 to 1.31)	0.69 (0.37 to 1.31)	0.59 (0.32 to 1.09)	0.40	0.92 (0.84 to 1.01)	0.083
OR (95%CI) ^b	1.00 (ref)	0.87 (0.41 to 1.87)	0.94 (0.43 to 2.02)	1.05 (0.50 to 2.18)	0.96	1.00 (0.90 to 1.12)	0.97
SICH							
N (%)	5/101 (4.9)	5/90 (5.6)	3/82 (3.7)	9/99 (9.1)			
OR (95%CI) ^a	1.00 (ref)	1.13 (0.31 to 4.08)	0.77 (0.17 to 3.37)	1.98 (0.63 to 6.23)	0.45	1.05 (0.89 to 1.25)	0.56
OR (95%CI) ^b	1.00 (ref)	1.25 (0.31 to 5.00)	0.59 (0.10 to 3.40)	3.02 (0.83 to 10.9)	0.15	1.11 (0.91 to 1.35)	0.30
PH							
N (%)	12/101 (11.9)	15/90 (16.7)	10/82 (12.2)	19/99 (19.2)			
OR (95%CI) ^a	1.00 (ref)	1.53 (0.67 to 3.50)	1.11 (0.45 to 2.76)	1.86 (0.84 to 4.10)	0.40	1.09 (0.97 to 1.22)	0.13
OR (95%CI) ^b	1.00 (ref)	1.71 (0.70 to 4.20)	1.05 (0.39 to 2.84)	1.75 (0.72 to 4.25)	0.46	1.04 (0.91 to 1.18)	0.55

^a adjusted for center and first-line thrombectomy strategy; ^b adjusted for center, first-line thrombectomy strategy, age, NIHSS, ASPECTS and IV rtPA; ^c p-values for comparison between SBP quartiles. ^d OR calculated per 10 mmHg increase in SBP. ^e p-values calculated using a logistic mixed regression model with SBP as continuous variable.

Table 3. Effect of diastolic blood pressure on outcomes

	DBP quartiles				p-value ^c	OR (95%CI) ^d	p-value ^e
	<70	70-80	80-90	>90			
Revascularization, TICI2b3							
N (%)	86/101 (85.1)	78/92 (84.8)	74/88 (84.1)	83/100 (83.0)			
OR (95%CI) ^a	1.00 (ref)	1.09 (0.48 to 2.49)	1.04 (0.46 to 2.36)	0.93 (0.43 to 2.04)	0.98	0.92 (0.77 to 1.10)	0.34
OR (95%CI) ^b	1.00 (ref)	1.05 (0.46 to 2.42)	1.17 (0.50 to 2.75)	0.95 (0.43 to 2.09)	0.97	0.92 (0.77 to 1.10)	0.35
Favorable outcome							
N (%)	32/87 (36.8)	48/88 (54.5)	44/79 (55.7)	36/86 (41.9)			
OR (95%CI) ^a	1.00 (ref)	1.86 (1.00 to 3.44)	2.09 (1.11 to 3.94)	1.19 (0.64 to 2.22)	0.064	1.00 (0.87 to 1.15)	0.99
OR (95%CI) ^b	1.00 (ref)	2.31 (1.10 to 4.85)	1.94 (0.91 to 4.13)	1.17 (0.56 to 4.56)	0.083	0.99 (0.84 to 1.18)	0.94
SICH							
N (%)	4/97 (4.1)	7/90 (7.8)	6/87 (6.9)	5/98 (5.1)			
OR (95%CI) ^a	1.00 (ref)	1.96 (0.54 to 7.02)	1.79 (0.48 to 6.63)	1.30 (0.33 to 5.04)	0.72	0.97 (0.73 to 1.28)	0.83
OR (95%CI) ^b	1.00 (ref)	2.85 (0.63 to 12.90)	2.83 (0.61 to 13.09)	2.07 (0.43 to 9.89)	0.53	0.99 (0.73 to 1.35)	0.96
PH							
N (%)	15/97 (15.5)	10/90 (11.1)	15/87 (17.2)	16/98 (16.3)			
OR (95%CI) ^a	1.00 (ref)	0.68 (0.29 to 1.61)	1.12 (0.51 to 2.47)	1.10 (0.51 to 2.39)	0.65	0.99 (0.83 to 1.19)	0.91
OR (95%CI) ^b	1.00 (ref)	0.58 (0.22 to 1.53)	1.47 (0.62 to 3.51)	1.24 (0.53 to 2.91)	0.27	0.98 (0.81 to 1.19)	0.86

^a adjusted for center and first-line thrombectomy strategy; ^b adjusted for center, first-line thrombectomy strategy, age, NIHSS, ASPECTS and IV rtPA; ^c p-values for comparison between DBP quartiles. ^d OR calculated per 10 mmHg increase in DBP. ^e p-values calculated using a logistic mixed regression model with DBP as continuous variable

